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**UNITED STATES DEPARTMENT OF COMMERCE**
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| APPLICATION NUMBER | FILING DATE | FIRST NAMED APPLICANT | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 08/286,189 | 08/05/94 | SANHUEZA | S MISMS1038348 |

| EXAMINER | |
|---|---|
| MASOUDD,K | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1802 | 7 |

DATE MAILED: 07/12/96

18N1/0712

SIM AND MCBURNEY
330 UNIVERSITY AVENUE
SUITE 701
TORONTO ONTARIO M5G 1R7 CANADA

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

## OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on April 4, 1996.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire _____ month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) 1-16 is/are pending in the application.

Of the above, claim(s) 17-19 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-16 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of Reference Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

-- SEE OFFICE ACTION ON THE FOLLOWING PAGES --

1. Applicants' amendment filed April 4, 1996 has been entered. Amended claims 1, 5 and 12 have been entered. Applicants' have withdrawn claims 17 to 19 from the instant application. Furthermore, applicant's have deleted claims 1-16 from application no. 08/472,174 to obviate double patenting rejection and pursuing claims 17-19. Claims 1-16 are pending in the instant application.

2. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description.

The properties of the immunogenic composition prepared by the claimed method are not clear. The claims are drawn to a method which involves inactivating a purified virus to obtain a composition containing a "non-infectious and immunogenic RS virus". One of skill in the art would interpret the composition of these claims as being a whole virus. However, it is not clear that the treatment of a purified respiratory syncytial (RS) virus with a non-ionic detergent would

result in a composition containing a whole virus or whether it would result in a composition containing solubilized viral proteins which resembles a subunit vaccine. Ewasyshyn et al teach that the viral envelope glycoproteins are solubilized by octylglucoside (i.e. n-octyl-β-D-glucopyranoside) (p 3). Ewasyshyn et al specifically disclose treating the pelleted virus for 1.5 hours with 2% v/v Triton X-100 and that alternately octylglucoside may be used (p 6). The specification teaches treating purified RSV with n-octyl-β-D-glucopyranoside (p 10). Specifically, the specification discloses treating the virus with 1% w/v n-octyl-β-D glucopyranoside for two hours. Therefore, it is not clear that the claimed method results in an inactivated whole RSV or whether it results in a composition consisting of solubilized RSV proteins. Because the non-ionic detergent would be expected to solubilize the viral proteins, the composition resulting from treating the purified virus with a non-ionic detergent would be a different composition than RSV treated with β-propiolactone or ascorbic acid and therefore the meaning of the terms "non-infectious and immunogenic RS virus" (claim 1) or "purified inactivated RS" when using non-ionic detergents as inactivating agents is not clear.

Applicant's changed the term virus to viral preparation and failed to overcome the above mentioned rejections. Applicants further argue that an objection to the specification and rejections under 35 U.S.C. § 112, first paragraph, is nothing more than lack of utility under 35 U.S.C. § 1o1 of co-pending application 08/472,174. Since the claims 1-16 are limited to this application and not to the co-pending application therefore, lack of utility under 35 U.S.C. § 1o1

has not been considered in the instant application. Therefore, claims 1-16 are further rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection.

The cotton rat model used by Applicants has been used with some success as a model for disease potentiation by formalin-inactivated RSV as taught by Chanock et al (p 140, column 1, second paragraph). Because Applicants' invention is also an inactivated RSV vaccine, the effect of these vaccines on pulmonary pathology could effectively be tested using the cotton rat model. However, the effectiveness of the vaccine based on results achieved in the cotton rat model may not necessarily be extrapolated to humans for the reasons which follow. McIntosh et al teach that although every subhuman primate species that has been examined can be infected by intranasal instillation of RSV, only the chimpanzee and owl monkey develop symptoms of infection. McIntosh et al also disclose that a satisfactory animal model of the lower respiratory tract illness seen most commonly in human infants has not yet been found (p 1051, column 2, paragraph 3). Collins et al disclose that the response to RSV infection in the chimpanzee most closely resembles that of humans with regard to the quantity and duration of virus shedding and the development of clinical disease (paragraph bridging pages 164 to 165). Collins et al teach that while nearly complete resistance to challenge with RSV infection was induced by immunization with vaccinia-RSV recombinants in cotton rats and owl monkeys, the vaccine had poor efficiency in chimpanzees (p 166, column 2). Collins et al also state that because of the permissiveness of the chimpanzees for RSV replication it seems likely that restriction of RSV replication would be more difficult to achieve in chimpanzees, and in infants and children, than in monkeys and

rodents. Collins et al continue by stating that information obtained solely from monkeys and rodents might provide an overly optimistic assessment of candidate RSV vaccines (p 167, column 2, paragraph 2). In a recent review article on RSV vaccines, Hall states the following:

> "Currently there is no accurate way to predict the response of infants to a candidate vaccine before actual administration. Are there measurable parameters that correlate with an immune response that is protective, durable or detrimental? We do not even know what type of immune response would be safe and protective in young infants. Evidence has accumulated that certain serum antibodies are beneficial and protective, but they are only one part of the collage of RSV immunity, as indicated by the virus's ability to infect some infants with high titers of maternal antibody." (p 1394, column 2).

Therefore, in view of the above teachings, protection observed in the cotton rat model cannot be extrapolated to humans. Due to the unpredictability of RSV vaccines to provide protection in humans, it would require undue experimentation to determine how to use the claimed vaccine compositions to provide protection in humans. Applicants' arguments have been considered in this context but are not deemed to be persuasive.

Claims 1-4 and 15-16 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth above in the objection to the specification.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure. In view of the potentiation of disease by the formalin-inactivated vaccine, it is not predictable whether the BPL-inactivated vaccine would have a similar effect thus making this form of inactivation unsuitable for use as a vaccine in humans. Chanock et al propose that the disease potentiation by the inactivated RSV vaccine appears to have occurred because formalin inactivation selectively reduces the antigenicity of protective epitopes present on the RSV F surface glycoprotein (p 139 column 2, paragraph 1). In an article on the action of BPL, Budowsky et al (Vaccine 9: 319-325) teach that the action of any chemical agent on viruses modifies not only the nucleic acid responsible for infectivity but also viral proteins and glycoproteins (p 321, column 2). Therefore, it would not be unexpected that BPL or ascorbic acid could similarly modify the RSV F surface glycoprotein and result in the potentiation of disease such as was observed with formalin. Neugebauer teach that although trends in the behavior of simple detergent/solvent system can be predicted from theory, no global explanation of the interaction of detergents with biomacromolecules exists. Neugebauer states that the task of finding the best detergent for a particular application is usually accomplished by trial and error (p 253, paragraph 2). Therefore, it is not predictable other non-ionic detergents would have the same effect on the RSV glycoproteins as octylglucopyranoside and whether the results of inactivation with other non-ionic detergents would be the same as octylglucopyranoside in terms of pulmonary pathogenicity. In the absence of evidence to the contrary, the ability of a BPL-inactivated, ascorbic acid-inactivated, or other non-ionic detergent-inactivated vaccines to provide

protection from RSV infection in humans without causing increased pathogenicity is unpredictable.

Claims 1-7, 9, and 10-16 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth above in the objection to the specification.

3. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was

commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-4, 15 and 16 are rejected under 35 U.S.C. § 103 as being unpatentable over Bordt et al in view of Downing et al and further in view of McIntosh et al.

Bordt et al teach a bovine respiratory syncytial virus which is inactivated with ascorbic acid column 2, lines 10-19 and column 6, lines 52-56). While Bordt et al is silent as to whether the virus is substantially free from cellular and serum components; Downing et al teach a method of preparing respiratory syncytial virus (RSV) which includes the following steps: 1) growing RSV on a cell line; 2) harvesting the grown virus; 3) purifying the virus under non-denaturing conditions to produce a virus substantially free from cellular and serum components (p 217-218 and 211). Bordt et al teach a vaccines against viruses, including paramyxoviruses, which are inactivated with ascorbic acid (column 2, lines 10-19). Bordt et al teach the administration of the vaccine to humans for preventing disease (column 1, lines 64-67). Bordt et al teach that the vaccine may include adjuvants (column 2, lines 41-45). Bordt et al do not specifically teach the route of administration or the population to which the vaccine is to be administered. Bordt et al also do not specifically disclose human respiratory syncytial virus. McIntosh et al teach that human respiratory syncytial virus is the most important cause of viral lower respiratory tract disease in infants and children and that human RSV is a paramyxovirus (p 1045).

It would have been obvious to one of ordinary skill in the art to inactivate human RSV for use as vaccine because Bordt et al teach that paramyxoviruses may be inactivated with ascorbic acid and RSV is a paramyxovirus as taught by McIntosh. It would have been obvious to administer the vaccine to the people in need of such a vaccine such as infants and children as taught by Mcintosh. Finally, oral, intranasal, or injectable forms and routes of administration would be obvious because vaccines are routinely administered in these ways.

Claims 5 and 6 are rejected under 35 U.S.C. § 103 as being unpatentable over Downing et al in view of Preston et al.

Downing et al teach a method of preparing respiratory syncytial virus (RSV) which includes the following steps: 1) growing RSV on a cell line; 2) harvesting the grown virus; 3) purifying the virus under non-denaturing conditions to produce a virus substantially free from cellular and serum components (p 217-218 and 211). The purification procedure involved ion exchange chromatography followed by sucrose gradient centrifugation (p 211, paragraph 2). Downing et al do not teach inactivating the virus with β-propiolactone.

Preston et al teach the inactivation of RSV by treatment with β-propiolactone (paragraph bridging p 819-820).

It would have been obvious to one of ordinary skill in the art to inactivate the RSV purified by the method of Downing et al with β-propiolactone because β-propiolactone is effective in inactivating RSV as taught by Preston et al. Furthermore, one of skill in the art would

inactivate a virus for an immunogenic composition to prevent the host from becoming infected with the virus.

Claims 5 and 9 are rejected under 35 U.S.C. § 103 as being unpatentable over Downing et al in view of White et al.

The teachings of Downing et al are set forth above. Downing et al do not teach inactivating the virus with ascorbic acid.

White et al teach the inactivation of RSV by treatment with ascorbic acid (paragraph bridging pages 529-530). White et al teach that the use of ascorbic acid as an inactivating agent has the advantages of being less expensive and more readily available than gamma radiation and is not carcinogenic as is β-propiolactone (p 530, paragraph bridging columns 1 and 2).

It would have been obvious to one of ordinary skill in the art to inactivate the RSV purified by the method of Downing et al with ascorbic acid because ascorbic acid is effective in inactivating RSV and has the advantages taught by White et al and set forth above. Furthermore, one of skill in the art would inactivate a virus for an immunogenic composition to prevent the host from becoming infected with the virus.

Claims 5, 7 and 8 are rejected under 35 U.S.C. § 103 as being unpatentable over Downing et al in view of Prince and Georgiades et al.

The teachings of Downing et al are set forth above. Downing et al do not teach inactivating the virus with a non-ionic detergent, specifically n-octyl-β-D-glucopyranoside.

Prince teaches the inactivation of plasma hepatitis virus by treatment with a non-ionic detergent and cite n-octyl-β-D-glucopyranoside as one of the detergents which may be used in the method (column 4, lines 37-39 and column 5, line 33). Prince teaches that the advantages of using non-ionic detergents is that they are non-denaturing and are not carcinogenic (sentence bridging columns 2 and 3). Georgiades et al teach the inactivation of contaminating viruses in interferon alpha solutions by treatment with non-ionic detergents (column 4, lines 1-16).

It would have been obvious to one of ordinary skill in the art to inactivate the RSV purified by the method of Downing et al with by treatment with n-octyl-β-D-glucopyranoside because non-ionic detergents are capable of inactivating viruses as taught by Prince and Georgiades et al and have the advantage of being non-denaturing to proteins and non-carcinogenic as taught by Prince. Furthermore, one of skill in the art would inactivate a virus for an immunogenic composition to prevent the host from becoming infected with the virus.

Claims 5, 10, 12 and 13 are rejected under 35 U.S.C. § 103 as being unpatentable over Ewasyshyn et al in view of Mbiguino et al.

Ewasyshyn et al teach a method of preparing respiratory syncytial virus (RSV) which includes the following steps: 1) growing the virus in a medium virtually free of exogenous serum proteins on a tissue culture cell substrate that is readily acceptable for use in human vaccine production (paragraph bridging p 3 and 4); 2) harvesting the virus; and 3) purifying the virus by, a) filtration to remove cell debris, b) concentration by tangential flow ultrafiltration using a 100 kD nominal molecular weight cut off membrane, and c) pelleting the ultrafiltered material by

ultracentrifugation (p 3, lines 10-13 and p 5, line 34 to p 6, line 9). Ewasyshyn et al do not teach further purifying the virus using sucrose density gradient centrifugation. Ewasyshyn et al do not teach inactivating the virus for formulation as an immunogenic composition.

Mbiguino et al teach purifying RSV under non-denaturing conditions using a sucrose gradient (p 163 third paragraph and p 165 first paragraph).

It would have been to purify RSV using the method taught by Ewasyshyn et al with a further step of sucrose density gradient centrifugation as taught by Mbiguino et al because sucrose gradient centrifugation is an effective means of preparing pure RSV and a highly purified virus would be optimal for an immunogenic composition to prevent the formation of antibodies against contaminating proteins. It would also have been obvious to inactivate the RSV for an immunogenic composition to prevent the host from becoming infected with the virus.

Claim 11 is rejected under 35 U.S.C. § 103 as being unpatentable over Ewasyshyn et al in view of Mbiguino et al as applied to claims 5, 10, 12 and 13 above, and further in view of McIntosh et al and Paradiso et al.

The teachings of Ewasyshyn et al and Mbiguino et al are set forth above. It would have been obvious to purify RSV using the method taught by Ewasyshyn et al with a further step of sucrose density gradient centrifugation as taught by Mbiguino et al for the reasons discussed above. It would also have been obvious to inactivate the RSV as discussed above. The above cited art do not specifically teach growing RSV on cells from the VERO cell line.

McIntosh et al teach that RSV may be successfully grown in VERO cells (p 1051, paragraph 2). Paradiso et al teach that highly immunogenic protein may be prepared from RSV grown in Vero cells (column 21, lines 1-30).

It would have been obvious to grow RSV in VERO cell lines as an alternative cell line for growing RSV because highly immunogenic proteins from RSV may be obtained from RSV grown in VERO cells as taught by Paradiso et al.

Claim 14 is rejected under 35 U.S.C. § 103 as being unpatentable over Ewasyshyn et al in view of Downing et al and Kuchler.

Ewasyshyn et al teach a method of preparing respiratory syncytial virus (RSV) which includes the following steps: 1) growing the virus in a medium virtually free of exogenous serum proteins on a tissue culture cell substrate (paragraph bridging p 3 and 4); 2) harvesting the virus; and 3) purifying the virus by, a) filtration to remove cell debris, b) concentration by tangential flow ultrafiltration using a 100 kD nominal molecular weight cut off membrane, and c) pelleting the ultrafiltered material by ultracentrifugation (p 3, lines 10-13 and p 5, line 34 to p 6, line 9). Ewasyshyn et al do not teach further purifying the virus using gel filtration and ion-exchange chromatography. Ewasyshyn et al do not teach inactivating the virus for formulation as an immunogenic composition.

Downing et al teach a method of purifying RSV using ion-exchange chromatography (paragraph bridging pages 217-218) Downing et al teach that gel filtration chromatography may be a useful complimentary technique for further purification after initial density gradient or

affinity purification steps (p 226, last paragraph). Downing also exemplifies a purification procedure which involves ion-exchange chromatography followed by sucrose gradient centrifugation to increase the purity (p 221)

Kuchler teaches that there are three basic steps to the purification of viruses (p 184-194). The first is clarification (p 185). The second is concentration which may be performed by several methods including ultrafiltration (p 185). The third step is purification. Kuchler teaches that purification of viruses may be accomplished by chromatograph and ion-exchange resins, by molecular sieving on gel filtration columns, by countercurrent distribution or by gradient centrifugation (p 186, paragraph 4).

It would have been obvious to one of ordinary skill in the art to employ gel filtration and ion exchange chromatography to the method taught by Ewasyshyn et al in order to obtain a more purified RSV preparation for use as an immunogenic composition to avoid the generation of antibodies to contaminating proteins. The steps taught by Ewasyshyn et al are basically clarification and concentration steps according to the purification scheme taught by Kuchler. Because Downing et al teaches that RSV may be purified using ion-exchange chromatography and that gel-filtration may additionally be employed in purification procedures, one of ordinary skill in the art would have been motivated to use these two procedures, which are well known methods in virus purification, to remove the serum components when purifying RSV. Downing et al teaches a gel filtration step following other chromatography methods. However, in the absence of evidence to the contrary, performance of the chromatography steps in either order would be expected to have similar results. As stated above, it would also have been obvious to

inactivate the RSV for an immunogenic composition to prevent the host from becoming infected with the virus.

Applicants' arguments have been considered but are not deemed to be persuasive and rejections are proper. In summary, applicants' argue that inactivated purified RS viral preparation free from contaminating cellular and serum proteins used as a vaccine to treat RSV infection in humans without causing enhanced pulmonary pathology. Applicant's further argue that art points away from the recited procedure and there is no motivation to use such steps. Several refernces have been cited above that teach such kind of steps and newly added reference by Murphey-Corb et al teach that "using a macaque model, a formalin-inactivated whole-virus vaccine and two subunit vaccines were tested for efficacy against SIV infection. Immunization with formalin-inactivation SIV protected 8 of 9 monkeys against viral infection following challenge with 10 animal infection doses. A glycoprtoein prepn. of detergent-disruption virions prevented infection and disease in only 2 0f 4 monkeys". Thus, it is clear that there is prior art that teaches use of inactivated virus as vaccine to treat infection. All claims 1-16 are rejected under 35 U.S.C. § 103 as being unpatentable over above cited references and further in view of Murphey-Corb et al .

Papers related to this application may be submitted to Group 180 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax number is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Khalid Masood whose telephone number is (703) 305-6998.

Any inquiry of general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Khalid Masood, Ph.D.

JAMES C. HOUSEL 7/10/96
SUPERVISORY PATENT EXAMINER
GROUP 180

July 8, 1996